REMARKS

Claims 1, 4-24, 28-32 and 36 are pending in this application, with claim 32 being withdrawn from consideration. Applicants cancel claims 4-6, 8-11, and 19-20, and amend claims 1, 12-14, 17, and 21. With entry of this amendment claims 1, 7, 12-18, 21-24, 28-31 and 36 are under consideration.

No new matter is presented by way of the amendments to the claims, which are submitted to more clearly focus prosecution on certain aspects of the invention previously recited in dependent claims. Applicants acknowledge that these amendments are submitted after final, and submit herewith a Request for Continued Examination. Applicants respectfully request entry of the amendments and reconsideration of the claims in light of following remarks.

RELATED APPLICATIONS

The Examiner's attention is drawn to co-pending application no. 11/734,464, naming the same inventor and owned by the same assignee as the instant application, and to co-pending application no. 11/573,128, owned by the same assignee as the instant application. The disclosures, claims and/or file histories of these applications may contain subject matter that is material to the instant application. Both of the foregoing applications are currently assigned to Examiner Kinsey's docket.

Claims 1, 7, 12-18, 21-24, 28-31 and 36 are non-obvious

Claims 1, 4, 5, 12, 13, 17, 18, 21, 22, 28-31 and 36 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Nabel *et al.* (WO 02/32943 ; hereinafter "Nabel"). To the extent that these rejections are maintained with respect to the amended claims, Applicants traverse.

Under 35 U.S.C. § 103, a patent may not be obtained if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated

reasoning with some rational underpinning to support he legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.* (550 U.S. ___, 127 S. Ct. 1727, 2007, 82 USPQ2d 1385, 1396).

In view of the Supreme Court's recent decision in *KSR Int'l v. Teleflex Inc.*, where the Examiner alleges that the claimed invention is a combination of prior art elements according to known methods, the Examiner must articulate the following:

> (1) a finding that the prior art included each element claimed, although not necessarily in a single prior art reference, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements in a single prior art reference:
> (2) a finding that one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely would have performed the same function as it did separately;
> (3) a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable; and
> (4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.
> Federal Register Vol. 72, No. 195: 57256, at 57529.

"If any of these findings cannot be made, then this rationale *cannot* be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art." *Id.* (emphasis added)

The hallmark of obviousness is predictability. A combination of prior art elements is obvious (or even obvious to try) if the combination does no more than yield predictable results. Conversely, it stands to reason that if the results of the combination are unpredictable (either inherently or technically), the combination is not obvious. Thus, the question to be asked in evaluating obviousness of the instant claims is not simply whether the individual elements of the claims can be found in the prior art, but whether their combination would have been predicted (or expected) to yield the desired results.

Claim 1 (as amended) is directed to: "[a] pharmaceutical composition comprising a polynucleotide that comprises a sequence encoding an HIV gp120 envelope protein operably linked to a heterologous promoter, wherein the gp120 encoding sequence is linked to a sequence encoding HIV RT and a sequence encoding HIV Gag and a sequence encoding HIV Nef to encode a gp120, RT, Gag and Nef-containing fusion protein and wherein the HIV gp120 envelope protein is lacking a functional secretion signal and is substantially non-glycosylated when expressed in a mammalian target cell, and at least one pharmaceutically acceptable

excipient, diluent, and/or carrier." The Examiner alleges that Nabel discloses "double stranded DNA vectors comprising sequences that encode an HIV Env that is non-glycosylated and HIV Env fused to another HIV gene such as Nef." (citations omitted) The Examiner further alleges that "[t]he teachings of Nabel et al. include the use of gp120 in the envelope-containing vectors and fusion proteins." (citations omitted) The Examiner also alleges that Nabel teaches compositions including the vectors and carriers and adjuvants, as well as methods for their administration. However, the Examiner does not suggest that Nabel teaches a gp120 envelope protein lacking a functional secretion signal.

Applicant disagrees. Although Applicants agree that Nabel relates to DNA vectors that encode an HIV Env protein fused to Nef (as exemplified on pages 58-59 of Nabel), Nabel does NOT in fact teach the use of gp120 is a fusion protein with Nef, or for that matter, with any other HIV protein. In particular, the teachings of Nabel et al. differ from the the subject matter of the instant claims in that the HIV Env protein taught by of Nabel et al. (*e.g.*, on pages 58 and 59, as well as elsewhere in this reference) are longer portions of the HIV Env protein. The smallest Env protein taught by Nabel et al. is a modified gp128 protein *with a deletion of the cleavage site that prevents the production of gp120.*

As stated in the instant specification (p. 2, lines 1-4), "[t]he gp120 protein is first expressed as a larger precurson molecule (gp160), which is then cleaved post-translationally to yield gp120 and gp41." Nabel et al. describe certain deletions in the gp160 (and/or gp150) protein that they indicate were designed to stabilize and expose functional domains of the protein. To generate the desired structure, "the cleavage site was removed to prevent the proteolytic processing of the envelope and stabilize the protein by linking it covalently to the gp41 extracellular and/or transmembrane domain." (p. 44, lines 3-10, citations omitted, emphasis added)

Thus, in the exemplary immunogens described by Nabel, the cleavage site that releases gp120 has been altered to eliminate proteolytic processing of the Env precursor to gp120 and retain the gp41 domain. Nabel further teaches that the gp41 is of particular importance in producing the desired structural and functional attributes. (Nabel et al., page 46). One of skill in

the art would immediately recognize that the term gp120 refers to a particular protein entity produced by cleavage of the HIV Env precursor, and that the proteins disclosed by Nabel et al., not only are NOT gp120, but are not processed to yield gp120.

Rather than suggesting any use of a gp120 protein, as indicated above, Nabel et al. suggests the use of longer fragments of the HIV Env protein. In particular, Nabel suggests that "a modified gp140 or a related derivative is envisioned to be a useful component of an AIDS vaccine." (page 4, lines 17-18). Thus, Nabel et al. differs from the subject matter of the current claims in that Nabel suggests that fragments of the HIV Env protein other than gp120 may be useful (*e.g.*, as component of a fusion protein) as a vaccine against HIV. Indeed, by advocating the use of longer Env proteins, such as an uncleavable gp140 and/or gp128 that cannot give rise to gp120, the disclosure of Nabel et al. teaches away from the use of the gp120 protein in a vaccine composition, such as in the context of a fusion protein.

More particularly, claim 1 of the instant application is directed to "a polynucleotide that comprises a sequence encoding an HIV gp120 envelope protein operably linked to a heterologous promoter, wherein the gp120 encoding sequence is linked to a sequence encoding HIV RT and a sequence encoding HIV Gag and a sequence encoding HIV Nef to encode a gp120, RT, Gag and Nef-containing fusion protein and wherein the HIV gp120 envelope protein is lacking a functional secretion signal and is substantially non-glycosylated when expressed in a mammalian target cell..." Although Nabel et al. refer to the use of various of their described proteins in the context of fusion proteins. Applicants are aware of no disclosure by Nabel et al. that specifically suggests gp120, RT, Gag and Nef together in a fusion protein. Indeed, where Nabel et al. discusses fusion proteins, *e.g.*, pages 47-50, this reference indicates that "full length Pol sequence is preferred for use in the fusion protein..." (page 49, lines 10-11). In any case, as discussed above in detail, to the extent that any Env-containing fusion proteins are suggested, such fusion proteins do not include gp120, but rather include a longer portion of the Env protein with different characteristics and attributes that gp120, and which cannot be processed to produce gp120.

Moreover, as admitted by the Examiner, nothing in Nabel et al. teaches any variant of gp120 Env that lacks a functional signal sequence. The Examiner alleges (on page 4 of the Office Action) that Li et al. teaches that non-glycosylated forms of HIV gp120 can be made by deleting the secretion signal of gp120, and such proteins are nonsecreted. The Examiner also alleges that Botarelli teaches that glycosylation residues on gp120 can function as hindering structures that limit antigen recognition by T-lymphocytes. Based on these documents, the Examiner contends:

> It would have been obvious to one of ordinary skill in the art to modify the polynucleotides taught by Nabel et al. to use HIV env. sequences lacking a secretory signal sequence to produced non-glycosylated HIV Env. One would have been motivated to do so, given the fact that deletion of the secretion signal is a routinely used method to produce non-glycosylated proteins. One also would have been motivated given the suggestion by Botarelli et al. that glycosylation residues on gp120 can function as hindering structures that limit antigen recognition by T-lymphocytes. There would have been a reasonable expectation of success, given the fact that it is well known that the removal of the secretory signal sequence bypasses the secretory pathway and the addition of carbohydrates, and that others have successfully produced non-glycosylated proteins by removing the secretory signal sequence. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art oat the time the invention was made.
> (p. 5, of Office Action)

Applicants respectfully disagree.

Nabel discloses "mutants in which conserved N-linked glycosylation sites were eliminated by site-directed mutagenesis of HIV Env" (*e.g.,* p. 43, lines 29-30) and "a series of internal mutations designed to replace the cleavage site (C), the fusion domain (F), and the interspace (I) between the two heptad repast all on a backbone of COOH-terminal truncations to expose the core protein of the viral membrane fusion protein Env..." (*e.g.*, p. 37, lines 16-20). The various constructs appear to be depicted schematically in Figure I. As shown in Figure I, all of the disclosed constructs include the N-terminal signal sequence of the native gp160 (gp120) protein.

Nabel also teaches that "[m]utations in highly conserved N-linked glycosylation sites did not significantly alter humoral or cellular immune response to native Env." (page 45, lines 31-

33), and that "[e]limination of conserved glycosylation sites did not substantially enhance humoral or CTL immunity." Indeed, Nabel concludes that "glycosylation mutants are unlikely to prove helpful" with DNA vaccination (*see*, page 46, lines 22-24). Thus, rather than teaching a skilled practitioner to use a DNA vaccine encoding a non-glycosylated Env protein, Nabel teaches the skilled practitioner to eschew a DNA vaccine encoding a non-glycosylated Env protein in favor of alternatives "with deletions in the cleavage site, fusion domain, and a region between the heptad repeats."

Thus, even if *arguendo*, one of skill in the art was motivated by Botarelli et al., and/or Li et al. to produce a non-glycosylated gp120, there is no logical nexus between the teachings of Nabel et al., and those of Li et al. and Botarelli et al. Because Nabel et al. teaches that modifying glycosylation of the Env protein is unlikely to be useful with DNA vaccination, one of skill in the art simply would not look to Li et al. or to Botarelli et al. to produce a DNA vaccine with an Env protein that lacked a signal sequence.

Li et al. discloses the production of glycosylated and non-glycosylated gp120 by transfecting SF9 cells with recombinant baculovirus encoding gp120 with and without a signal sequence, respectively. Li et al. teaches "that positively charged amino acids in the antural signal sequence of HIV-1 gp120 were crucial in the expression level, glycosylation, and secretion of glycosylated gp120. Deletion of ths signal sequence of HIV-1 gp120..., results in the synthesis of large quantities of a nonglycosylated and nonsecreted form with an apparent molecular mass of 53 kDa (p52)."

Botarelli et al. disclose polynucleotides that are useful for the production of protein (HIV Env) antigens. At no point does Botarelli et al. teach that the disclosed polynucleotides can be used in pharmaceutical compositions, *i.e.*, as DNA vaccines. The constructs of Botarelli et. al. are designed for expression in yeast, and utilize yeast promoters, which one of skill in the art would not be likely to select for a DNA vaccine (*e.g.*, yeast pyruvate kinase (*pyk*), glyceraldehydes-3-phosphate dehydrogenase (GAPDH)). (Details of the constructs and production are found in Barr *et al.*, *Vaccine* 5:90-101, 1987, reference 6 of Botarelli et. al.). In order to obtain the protein antigens, the yeast cells were harvested and the cells disrupted with

glass beads, prior to solubilizing and denaturing in SDS, and then concentrating and purifying the expressed Env proteins.

Additionally, contrary to the Examiner's allegation, Botarelli et al. teach that immunization with a non-glycosylated Env protein produced in yeast elicits an immune response in which a significant proportion of the T cells are unable to recognize native glycosylated gp120, because the glycosylation of the viral protein interferes with recognition by the T cells. This is clearly different (and, indeed opposite) from suggesting that glycosylated residues on gp120 in a vaccine act as hindering structures that limit antigen recognition by T-lymphocytes. Thus, Botarelli cannot be viewed as providing a motivation to vaccinate with a non-glycosylated form of Env any more than can Nabel. Nor can Botarelli be viewed as providing a reasonable expectation that such a vaccine would be successful for the reasons discussed above.

The production processes utilized by both Li et al., and Botarelli et al., and indeed the recombinant production of protein antigens is wholly non-analogous to DNA vaccines, and one of ordinary skill in the art would not look to recombinant production in yeast or insect cells to guide the modification of polynucleotide vaccines because the recovery method is wholly inapplicable. Furthermore, Nabel teaches consistently that expression of the Env protein *in vivo* in the host cell is important, and discloses that the variant of Env that "induced the greatest antibody response, is released in a soluble form." (*see*, p. 46, lines 9-10). Thus, a practitioner of ordinary skill in the art would not have found it obvious to to use a polynucleotide that encoded an Env protein that could not be secreted by the host cell (as taught by Li et al., and by Botarelli et al.) to produce a non-glycosylated antigen *in vivo* in the context of a DNA vaccine.

Furthermore, the claims as amended are directed specifically to polynucleotides that encode fusion proteins that include a non-glycosylated gp120 linked to RT, Gag and Nef. Such proteins simply are not taught by Nabel et al. Nor are such fusion proteins an inherent or necessary implication of Nabel et al., which particularly describes various fusion proteins, none of which include gp120, and none of which include in addition to Env: RT, Gag and Nef. Accordingly, Nabel et al., Li et al., and Botarelli et al., either alone or in any combination, do not

teach all of the elements of the invention of claim 1. Nor, for the reasons stated above, can these references render obvious claim 1, and claims dependent therefrom.

As stated in the instant specification, Applicants surprisingly discovered that in the context of a DNA vaccine, "a DNA vector expressing gp120 without a secretion signal and which is thus not glycosylated or secreted from the cell is a more effective stimulator of CTL responses than a DNA vector expressing gp120 with its native secretion signal." (page 7, lines 7-10, of the instant specification). Applicants respectfully remind the Examiner that it is impermissible to use "knowledge gleaned only from applicant's disclosure" in making an obviousness rejection. *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). Given the cumulative teaching in the cited art that would lead a skilled practitioner away from the production of pharmaceutical compositions including polynucleotides that encode an HIV gp120 lacking a secretory signal, it is only Applicants' disclosure that provides the basis for producing the compositions of claim 1 (and claims dependent therefrom).

Claims 15 and 16 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Nabel et al. in combination with Catchpole (WO 02/36792). Nothing in Catchpole, remedies the deficiencies of Nabel et al. in combination with either or both of Li et al. and Botarelli et al. Thus, these combinations of references cannot render obvious claims 15 and 16, which incorporate all of the limitations of amended claim 1.

Claims 23 and 24 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Nabel et al. in combination with Farina et al. and Roy et al. The Examiner alleges that Farina et al. and Roy et al. teach the use of adenovirus vectors. However, nothing in these references remedies any of the other deficiencies of Nabel et al., Li et al., or Botarelli et al., and their combination does not render obvious claims 23 and 24, which incorporate all of the limitations of amended claim 1.

Claims 1, 4 and 12 stand rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Jiang et al., in view of Botarelli et al. The Examiner alleges that Jiang et al. teaches an HIV gp120-gag fusion protein antigen expressed from a yeast expression vector. The Examiner does not suggest that Jiang et al. teaches a fusion protein that also includes RT and Nef. Thus, the

combination of this reference and Botarelli et al. do not teach the limitations of claim 1, either alone or in combination. Furthermore, As discussed above, one of skill in the art would not look to a construct or method for producing an gp120-containing fusion protein in yeast for the purpose of producing a DNA vaccine suitable for humans. Similarly, as discussed above, Botarelli et al., do not, in fact, suggest that such constructs be modified to eliminate glycosylation, since the cited passage refers to interference by glycosylated residues on infectious virus, and points to a potential immunological drawback of non-glycosylated antigens. Nor does the Examiner indicate why one of skill in the art would expect that modifying such a construct by eliminating the signal sequence would render such a polynucleotide suitable as a DNA vaccine (*e.g.*, that encodes a protein expressable and secretable in human cells). Again, Applicant respectfully submits that the Examiner is piecing together unrelated, insufficient and contrary references based on the impermissible use of Applicant's own disclosure, and the rejection should be withdrawn.

In view of the foregoing remarks, Applicants submit that the claims are not obvious, and the rejections under 35 U.S.C. § 103(a) should be withdrawn.

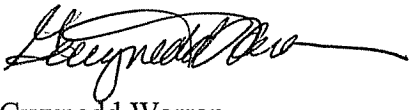
Double Patenting

Claims 1, 4-24, 28-31 and 36 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being allegedly unpatentable over claims 1-20, 24-27 and 32 of copending Application No. 11/734,464. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicant respectfully requests deferral of the issue of double patenting until such time that the claims in this application or the claims in copending Application No. 11/734,464 are found to be otherwise allowable.

Conclusion

On the basis of the amendments and remarks above, Applicants believe that the claims are now in condition for allowance. In the event that additional substantive issues remain, Applicants respectfully request that the Examiner contact their undersigned attorney to arrange a telephonic interview prior to the preparation of any further written action. Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification.

Respectfully submitted,



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